

ISOQUINOLINE DERIVATIVES HAVING KINASE INHIBITORY ACTIVITY  
AND MEDICAMENT CONTAINING THE SAME

This application is a 371 of PCT/JP03/11733 filed 9/12/2003.

BACKGROUND OF THE INVENTION

5 Field of the Invention

The present invention relates to derivatives having  
Rho kinase inhibitory activity, more particularly serine derivatives  
useful for the treatment of diseases mediated by Rho kinase.

Background Art

10 It has been revealed that Rho is activated upon the receipt of  
signals from various cell membrane receptors, and the activated Rho  
functions, through ROCK/Rho kinase and, further, actomyosin system, as  
a molecular switch of a wide variety of cellular phenomena such as  
smooth muscle contraction, cell movement, cell adhesion, change in  
15 character of cells (formation of actin stressed fibers), control of cell  
division (sthenia of cytokinesis or activation of gene transcription),  
platelet aggregation, leukocyte aggregation, cell proliferation, sthenia of  
carcinogenesis and invasion of cancer and the like.

The contraction of smooth muscle is deeply involved in the  
20 pathology of hypertension, angina pectoris, vasospasm, for example,  
cardiovascular contraction and cerebrovascular contraction, asthma,  
peripheral circulatory disorder, threatened premature birth, glaucoma,  
constriction of visual field, pollakiuria, impotence and the like. Cell  
movement plays an important role in invasion/metastasis of cancer,  
25 arteriosclerosis, retinopathy, immune response and the like. Cell  
adhesion is deeply involved in metastasis of cancer, inflammation, and  
autoimmune diseases. The change of cell morphology is deeply involved  
in cerebral dysfunction, osteoporosis, microbism and the like. Cell  
proliferation is deeply involved in cancer, arteriosclerosis and the like.  
30 Thus, Rho is deeply involved in various diseases.

ROCK or ROCK I (Japanese Patent Laid-Open No. 135683/1997;  
and T. Ishizaki et al., EMBO J., Vol. 15, No. 8, pp 1885-1893 (1996)) and  
Rho kinase or ROCK II (Japanese Patent Laid-Open No. 113187/1998;  
and T. Matsui et al., EMBO J., Vol. 15, No. 9, pp 2208-2216 (1996)) were  
35 reported as serine/threonine kinase which is activated upon the  
activation of Rho and were shown to be isozymes (O. Nakagawa et al.,